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Abstract

Estimates of healthcare costs for incident bronchiectasis patients are currently not available for any European country. Out of a sample of 4,859,013 persons covered by German statutory health insurance companies, 231 new bronchiectasis patients were identified in 2012. They were matched with 685 control patients by age, gender and Charlson Comorbidity Index and followed for 3 years.

The total direct expenditure during that period per insured bronchiectasis patient was €18,634.57 [95%CI: €15,891.02–€23,871.12], nearly one third higher (ratio of mean 1.31 [95%CI: 1.02–1.68]) than for a matched control (*P*<.001).

Hospitalization costs contributed to 35% of the total and were more than 50% higher in the bronchiectasis group (1.56 [95%CI: 1.20–3.01]; *P*<.001); on average, bronchiectasis patients spent 4.9 more days [95%CI: 2.27–7.43] in hospital (*P*<.001). Antibiotics expenditures per bronchiectasis outpatient (€413.81) were nearly five times higher than those for a matched control (4.85 [95%CI 2.72–8.64]).

Each bronchiectasis patient had on average 40.5 [95%CI: 17.1–43.5] sick leave days and induced work-loss costs of €4,230.49 [95%CI: €2,849.58–€5,611.20].

The mortality rate for bronchiectasis and matched non-bronchiectasis patients was 26.4% and 10.5%, respectively (*P*<.001).

Although bronchiectasis is considered underdiagnosed, the mortality and associated financial burden in Germany are substantial.

Keywords: burden of illness; costs; cost analysis; bronchiectasis; mortality

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Introduction

Bronchiectasis is characterized by irreversibly dilated airways leading to chronic bacterial infection which leads to persistent productive cough, hemoptysis, shortness of breath and chronic fatigue. Patients also experience episodes of exacerbations [1]. Importantly, chronically infected patients, especially those infected with *Pseudomonoas aeruginosa*, may have reduced quality of life, require more frequent hospitalizations and carry significantly higher risk of death [2].

Pulmonary diseases other than cystic fibrosis (CF) may predispose patients to bronchiectasis, which is then referred to as non-cystic fibrosis bronchiectasis [3]. Whilst in up to 32-50% of bronchiectasis cases, no underlying conditions can be identified [3,4], recognized causes include lung infection by nontuberculous mycobacteria [5], connective tissue diseases [6,7], and allergic bronchopulmonary aspergillosis (ABPA) [8]. Many patients with bronchiectasis will initially be diagnosed with chronic airflow limitation [9] and thus may be misdiagnosed as chronic obstructive lung disease (COPD). On the other hand, bronchiectasis may be a secondary complication of asthma and COPD: As recently described by *Quint* et al. [10], 42.5% of bronchiectasis patients in the UK had a coexisting diagnosis of asthma and 36.1% had a coexisting diagnosis of COPD.

Although bronchiectasis has previously been classified as an “orphan disease,” its incidence is now considered to be increasing worldwide [10,11]. As more patients require appropriate management, it is necessary to assess the resource requirements for treatment of bronchiectasis within the various European healthcare systems. However, estimates of healthcare costs for newly diagnosed bronchiectasis patients are currently not available for any European country. Therefore, the objective of the current study was to estimate the burden of illness associated with incident bronchiectasis in Germany.

Methods

Setting and Data Collection

This study was a population-based cohort study with a nested case-control design, based on administrative data from statutory company health insurance (SHI) funds from all regions of Germany. The data were provided to us by the database service provider sgh consulting, Hamburg (www.sgh-consulting.de). The health claims database of that company comprises anonymized billing data from longitudinally linked records of 4,850,013 insured persons (effective date: 31 July 2017) and is representative with respect to age and sex for the around 70 million Germans mandatorily insured under the SHI scheme. Patients with bronchiectasis were identified based on the 10th revision of

the International Classification of Diseases (ICD-10) GM (German modification) code J47. Patients classified as having newly diagnosed bronchiectasis were identified in the year 2012 and tracked over 3 years after the first (index) quarter in which J47 was coded.
Patients were classified as having incidental bronchiectasis if they met the following criteria: (a) at least one medical claim with a documented ICD-10 GM code J47 as an inpatient or with a verified diagnosis as an outpatient and (b) no documented ICD-10 GM code J47 in the eight quarters prior to the index quarter in 2012. (**Figure 1**). Patients with bronchiectasis who either had an ICD-10-GM diagnosis code E84.- (cystic fibrosis) or Q33.4 (congenital bronchiectasis) were excluded.

For calculating the increase in healthcare costs attributable to the presence of bronchiectasis, control patients without bronchiectasis were randomly assigned an index quarter in 2012 according to the distribution of index quarters in bronchiectasis patients. These were followed for the period of a total of 3 years without limitation to a calendar year, or until death. The control group was matched to the group of bronchiectasis patients at a ratio of 3:1 in regard to age, gender and in terms of their distribution and level of comorbidities. Therefore, patients' comorbidities were assessed and measured using the Charlson Comorbidity Index (CCI) score, a claims-based measure of overall disease burden based on the occurrence of at least one of 17 comorbidities identified using the ICD-10 GM coding manual [12, 13], and the frequency of comorbidity patterns of the matched non-bronchiectasis sample were as closely related as possible to those of the bronchiectasis patients.
As some diseases are known to be extraordinary cost drivers and therefore may bias the results of the study, bronchiectasis patients as well as control patients were excluded *a priori* if they suffered from one of the diseases that exceeded an amount of €20,000 in allocation according to the German morbidity-based risk structure equalization ("high-cost cases") [14].
Costs over the entire follow-up period were retrieved for five different categories: inpatient care (hospitalization), outpatient visits and diagnostics, prescribed pharmaceuticals according to German national drug (ATC) codes, remedies (physiotherapy treatments and modalities, such as active cycle of breathing and postural drainage techniques), medical aids (especially nebulizers and respiration therapy equipment) and sick pay. Furthermore, the top twenty prescribed drugs for bronchiectasis management were analyzed and compared to those of the non-bronchiectasis group.

Calculation of Loss of Productivity due to bronchiectasis (Indirect Costs)

In accordance with the human capital approach, indirect costs refer to the productivity loss for the national economy caused by absence from the workplace on sick leave.
According to the German Hanover Consensus [15] the per-day average productivity loss figure used to cover the self-employed income as well is calculated as: sick leave days × (gross income from non–self-employed work for the respective year/ 365 days).
The follow-up time period after diagnosis of a bronchiectasis patient amounts to a maximum of 36 months. As per-day employer cost for employee compensation in Germany increased slightly but continuously from 2012 (2012: €101.19; 2013: €103.28; 2014: €106.18; 2015: €108.74 [16]) our assessment considered the exact calendar year within which the observation period of an individual bronchiectasis patient or a matched control was on sick leave. We multiplied the amount of per-day employer costs of a given year between 2012 and 2015 with the number of lost working days of the patients in the respective year to arrive at our total amounts.

Statistical Analysis

Frequency and percentages were reported for categorical variables. For descriptive analyses, mean, standard deviation (SD), 95% confidence interval (CI), and median were reported for all continuous variables. To compare bronchiectasis patients and matched controls, appropriate univariate tests (i.e., chi-squared test of independence for categorical variables and the Wilcoxon-Mann-Whitney test for continuous variables) were used. Differences were considered significant if the two-sided *P*-value was less than .05. Ratios of the mean (RoM), including 95% confidence intervals, were calculated for continuous outcomes.
Mortality was determined separately between both groups yearly and at the end of the study period. We generated a Kaplan-Meier survival plot and used a log-rank test to prove whether the difference in survival times between the bronchiectasis and the non-bronchiectasis group was statistically significant. Cox regression, adjusted to group membership (bronchiectasis or non-bronchiectasis), age, and presence of COPD as comorbidity, was employed to calculate the Hazard Ratio (HR) of all-cause mortality
All costs are reported in Euros (€) in 2012 and the respective follow-up years in which they were incurred.

Results

Patient characteristics

After exclusion of four “high-cost” cases, two out of the bronchiectasis and two out of the control group, a total of 231 bronchiectasis cases and 685 matched controls met the study criteria and were included in the analysis. The mean age of bronchiectasis patients and of matched controls was 58.6 years [95%CI: 56.3–60.9], and 58.5 years [95% CI: 57.2–59.8), respectively. 61.5% of the patients were male and 39.5% were female. Patient´s mean CCI total score was equally high among both groups with 2.70 [95% CI: 2.4–3.0) in the bronchiectasis group and 2.76 (95% CI: 2.6–2.9) in the matched control group.

With respect to the most frequently represented diseases out of the range of predefined comorbid conditions in the CCI, more bronchiectasis patients (128/231, or 55.4%) than matched controls had the diagnosis COPD (J44.-) (**Table 1**). Nevertheless, COPD was also the most frequent comorbid condition (246/685, or 35.9%) in the control group. There were no significant differences between the two groups in the frequency of asthma (J45.-; 28.1% of the bronchiectasis patients and 27.0% of the controls), and in the frequency of gastroesophageal reflux disease (K21.-; 14.7% of all cases in both groups). Coronary heart disease (I25.-) was observed in 15.6% and 15.3%, respectively, and heart failure (I50.-) in 11.7 and 10.1%.

Incidence of bronchiectasis

The age- and gender-adjusted incidence rate for bronchiectasis in 2012 was 6.1 per 100.000 insured German inhabitants [95%CI: 6.0–6.3] (**Table 2**), whereby males aged over 65 years contributed mostly with an incidence of 21.68 [95%CI: 20.57– 22.86] per 100.000 persons of that age group.

Direct Costs

For patients with bronchiectasis, the total direct expenditure over the follow-up period per insured patient was €18,634.57 [95%CI: €15,891.02–€23,871.12], which was nearly one third (RoM 1.31 [95%CI: 1.02–1.68] higher than the expenditure for a matched control (€14,236.99 [95% CI: €11,318.77–€17,155.21]); *P*<.001 (**Table 3).** 47.6% of the bronchiectasis patients were hospitalized at least once during follow-up, and more than one third, or 34.9%, of the total cost (€6504.37 [95%CI: €5,098.02–€7,909.82]) could be attributed to costs accrued in the hospital sector. Whilst the diagnostic and drug costs in the outpatient setting did not differ between bronchiectasis patients and matched controls, hospital costs were 56% higher in the bronchiectasis group (RoM 1.56 [95%CI: 1.20–3.01]; *P*<.001). It was striking that bronchiectasis patients were more often (62%) prescribed mucoactive therapies, and that the costs of those agents were nearly 5 times higher in bronchiectasis patients with €70.11 per bronchiectasis patient versus €14.15 per control

patient (RoM 4.96 [95%CI: 4.91–5.28]; *P* =.001). Also the costs of medical aids, especially inhalation and home ventilation devices, were nearly three times higher in bronchiectasis patients (RoM 2.75 [95%CI: 1.95–3.90]; *P*<.001) (Table 3). On average, bronchiectasis patients spent 4.85 more days [95%CI: 2.27–7.43] in hospital during the observation period (**Table 4**).

The major part of the direct total costs, however, were drug costs in the outpatient setting accumulating to €7694.56 [95%CI: €5,354.77–€9,944.35], which accounted for 41.3% of total direct costs. On average, the frequency of visits per bronchiectasis patients to a chest physician was 83% higher (2.51 [95%CI: 2.34– 2.90] versus 1.37 [95%CI: 1.24 –1.50]; *P*<.001) and visits to a radiologists were also 28% higher (2.89 [95%CI: 2.57–3.03] versus 2.26 [95%CI: 2.12–2.35; *P*<.001]) within the 3-year follow-up period (**Table 4**).

Antibiotic Treatment

Of the 231 patients with newly diagnosed bronchiectasis, 88.2% were prescribed any type of antibiotics in the outpatient setting during the entire 3-year follow-up period, but only 59.7% patients of the matched control group (*P*<.001). In total, costs of antibiotics for bronchiectasis outpatients amounted to €87,728 and €56,219 for the matched control patients. Out of a total 861 prescriptions, fluoroquinolones were the most prescribed antibiotics in bronchiectasis patients (326 prescriptions, or 37.9%) followed by aminopenicillin (187 prescriptions, or 21.7%) and macrolides (90 prescriptions, or 10.5%). Overall, only 8 bronchiectasis patients (0.35%) and none of the control patients received inhaled antibiotics (all colistin) during the observation period. Thirteen out of the 231 patients (5.6%) received monotherapy with clarithromycin or azithromycin for at least two subsequent quarters, indicating that this therapy was administered for maintainance treatment of bronchiectasis rather than for treating other respiratory infections. Of note, parenteral antibiotics (eg, amikacin, ceftazidime or imipenem) were not prescribed for any bronchiectasis patient in the outpatient setting.

Treatment with bronchodilators

Costs of inhaled bronchodilators (ATC-R03) per bronchiectasis patient, of which salbutamol and long acting beta-2 agonists, such as salmeterol and formoterol, had particularly often been prescribed, were nearly 50% (RoM 1.49% [95%CI 1.37-1.52]) higher than in the matched controls (€1,595.42 [95%CI: €1,444.99–€2,048.6] versus €1,069.03 [95%CI: € 917.46–€1,136.46). 82.1% of bronchiectasis patients, but only 56.3% of the matched controls claimed at least one ATC-R03 prescription during the 3-year follow-up period.

Treatment with other drugs

As expected, costs of mucoactive drugs during the observation period were significantly higher (nearly 5 times) with €70.11 per bronchiectasis patient versus €14.15 per control patient (4.96 [95%CI: 4.95–4.98]; *P*<.001) and costs of topical nasal corticosteroids were nearly 4 times higher with €21.57 versus €6.06 (3.56 [95% 3.55–3.58]; *P*<.001].

Ranking of drugs prescribed for bronchiectasis patients and matched controls

As can be seen in **Table 5**, drug prescriptions in both groups focused on long-acting beta-2 agonists (LABA), used with or without inhaled steroids, and the antibiotics amoxicillin, ciprofloxacin and cefuroxime axetil. Significant differences between bronchiectasis patients and their matched controls could only be found with respect to the use of azithromycin and aclidinium bromide, the latter being a long acting muscarinic agent which before 2012 had not been approved in the EU for treating COPD.

Mortality

Differences in all-cause mortality rates per year between the three groups of bronchiectasis patients with COPD, without COPD and matched controls are shown in **Figure 2.** Sixty-one of the initial 231 diagnosed patients in the bronchiectasis group (26.41%), but only 72 of the initial 651 patients in the control group (10.5%), died within the 3-year follow-up period (**Table 6**, *P*<.0001, log-rank test). When using Cox´s regression and only adjusting for disease group, bronchiectasis patients had a nearly fourfold higher risk of death (HR: 3.64; 95%CI: 2.28–5.77; *P*<.0001). When adjusting for age, gender and the presence of COPD as co-morbidity, gender and the presence of COPD had no significant influence on the hazard ratio, whilst bronchiectasis patients had a relative 5.8 % increase in mortality rate per life year compared to the matched controls.

Cost due to Loss of Productivity

bronchiectasis patients had on average 40.5 [95%CI: 17.1–43.5] sick leave days during the follow-up period and induced indirect costs of €4,230.49 [95%CI: €2,849.58–€5,611.20]. However, for the same period also in the matched controls 45.7 [95%CI: 39.5-51.9] sick leave days and a productivity loss of €4,776.50 [95%CI: €4,127.84–€5,425.15] were found. Cost due to absenteeism from work amounted to €1,916.43 per bronchiectasis patient in the first year of follow-up and decreased slightly to €1,273.61 by the third year. Considering that total direct medical costs of bronchiectasis patients amount to €18,634.57, work-loss

costs in bronchiectasis patients are 25.6% of that amount. The work absence burden for employees with bronchiectasis was not significantly different from that for matched controls.

Discussion

The objective of this study was to provide the first comprehensive estimate of the economic burden of incident bronchiectasis bronchiectasis in any European country. This was accomplished by a retrospective observational design comparing medical and productivity-related expenditure for 231 bronchiectasis patients to a 1:3 matched comparison group of 685 control patients without bronchiectasis over a period of three years in Germany. The economic burden attributed to bronchiectasis is expected to be great, because it is a chronic disease that may require frequent medical consultations, long-term treatment with multimodal regimens, and hospitalizations for pulmonary exacerbations in order to minimize the risk of further progression. However, to date, published annual cost data for treatment of bronchiectasis are sparse:

The studies of Sanchez et al. [17] and de la Rosa et al. [18], which retrospectively determined the hospital costs of bronchiectasis in Spain (cost year 2013), reported mean costs of €4,672 ± €6,281 per patient [17] or €3,515 for patients with bronchiectasis as a primary diagnosis and €4,559 for patients with a secondary diagnosis [18]. Three North American studies calculated the annual costs of prevalent bronchiectasis patients ranging from US$13,244 (cost year 2001) [19] to over US$37,030 (in patients with exacerbation, 2008–2011 [20]) and up to US$67,764 (in patients with *Pseudomonas aeruginosa,* 2007–13 [21].

With respect to incident bronchiectasis patients, only the study of Joish et al. [22] examined the increase in resource use and costs for patients with bronchiectasis before and after the first year of diagnosis. US MarketScan Research data were analyzed for the period from 2005 to 2009 for patients diagnosed with bronchiectasis (n = 9,146) and controls without bronchiectasis (n = 27,438) who were matched to each bronchiectasis patient based on age, gender, geographic region and type of health plan enrolled in an 3:1 ratio. This resulted in an increase of US$2,319 per bronchiectasis patients in the 1st year after diagnosis, but of only US$1,607 for control patients. However, in contrast to our study, where COPD as one of the most important associated condition of bronchiectasis was explicitly allowed in both bronchiectasis cases and control patients, individuals with COPD were excluded if the claim was either 12 months prior (baseline) or during the subsequent 12-month follow-up period.

To our knowledge, our pilot study represents the first investigation of healthcare resource use and costs brought about by incident bronchiectasis cases worldwide who were matched

according to type and severity of their comorbidities and for which accumulated post-diagnosis costs have been followed for several years. Furthermore, it includes – for the first time – both mortality and costs due to lost patient productivity.

When considering only respiratory-related resource utilisation, bronchiectasis outpatients sought 80% more often specialized respiratory care, were 30% more often referred to radiologists (see **Table 4**). Based on records for the 25 most-prescribed drugs for both groups, we found no notable difference between the two groups in prescription patterns for antibiotics addressing exacerbations (fluoroquinolones, aminopenicillins and macrolides) nor for bronchodilators (predominantly salbutamol and LABAs) (see Table 5). In total, however, bronchiectasis patients received 27% and 29% more frequently prescriptions for bronchodilators and antibiotics, respectively, than was the case with controls (all $P<.001$).

Beyond the expected economic burden on the healthcare system, mortality in our bronchiectasis group after 3 years of follow up was surprisingly high at 26.4%. Whilst in Cox´s regression the presence of COPD had no significant influence on mortality when comparing the bronchiectasis group and the whole matched control group in which also a considerable proportion of patients (35.9%) had COPD, mortality in the bronchiectasis group was nearly four times higher (HR 3.73; 95%CI: 2.52–5.53) than in the COPD-free part of the matched patient group. This is in line with recently published evidence [23] that mortality may be higher among those who also had COPD than in patients with bronchiectasis alone. Because mortality in the bronchiectasis group was highest at 8.23% [95%CI: 5.33–12.49] within the first year following diagnosis, immediate and appropriate medical treatment should be offered as complications may arise.

Apart from the contribution of COPD, we were not able to investigate the reasons for the high mortality found among bronchiectasis patients. It may, however, be speculated that – regular chest x-ray being generally insensitive to the changes caused by bronchiectasis – high resolution computer tomography (HRCT), the radiological investigation of choice, was performed too late. Thus, a considerable fraction of bronchiectasis patients may have been chronically infected with bacterial pathogens well before the diagnosis of bronchiectasis was made. Unfortunately, we could not evaluate *P. aeruginosa* infection in our study sample as ICD-10 coding of bacterial pathogens is voluntary in Germany and therefore not routinely performed by physicians in the outpatient setting where more than 90% of bronchiectasis patients are cared for [9]. According to data from the representative German Bronchiectasis Registry PROGNOSIS (The PROspective German NOn-CF bronchiectaSIS patient

registry) which is part of the European Bronchiectasis Initiative EMBARC [24] and which currently has recruited more than 1000 patients, *P. aeruginosa* is the most prevalent pathogen during stable disease and during pulmonary exacerbations with detection rates of 30% and 36% respectively [25]. A high proportion of bronchiectasis patients [40.3% (93/231)] were hospitalized at least once in the first year following diagnosis. This observation suggests that the sicker patients whose disease was already fairly advanced at diagnosis may have started treatment with medication that proved at least partly ineffective with regard to the prevention of severe exacerbations requiring hospitalizations. This may have contributed to the poor prognosis of these patients within the follow-up period.

We also took into account reduced productivity caused by ongoing symptoms and exacerbations of bronchiectasis, which amounted to €1,916.43 per bronchiectasis patient the first year of follow-up and decreased slightly to €1,273.61 in the third year. As the total cost of €4,230.39 per bronchiectasis patient due to absenteeism from work that occurred within the 3 years of observation accounted for 22.7% of the burden caused by direct total costs, indirect costs may be considered to have a substantial economic impact on healthcare. Because short-term disability with sick leave days of less than 3 days is not captured by the SHI, these costs are most certainly underestimated in our calculations. The importance of indirect costs in bronchiectasis patients is not diminished by the fact that these did not differ significantly from the indirect costs in the matched control group, which was characterized not only by an equally high percentage of COPD (35.9%) but also by a comparable prevalence of cardiac comorbidities and asthma.

When extrapolating our age- and gender adjusted incidence rate for bronchiectasis of 6.1 per 100.000 insured German inhabitants (with a 95% confidence interval between 6.0 and 6.3) and keeping this incidence rate constant, on average a total of 5045 (4962 at minimum and 5210 at maximum) newly diagnosed bronchiectasis patients per year can be expected in the 2017 German population of 82.7 million [26], whereby males aged over 65 years, probably due to a high rate of concomitant COPD, are the most strongly represented bronchiectasis subpopulation.The annual direct and indirect expenditures attributable to the disease can be expected to amount to more than €38.45 million per year (€37.82 million at minimum and €39.71 million at maximum).

Our analysis was limited by several factors. First, we only followed bronchiectasis patients for 3 years after the quarter when the diagnosis was established and thus did not capture

the long-term burden of the disease. Accordingly, future studies of the long-term costs of bronchiectasis that also take the burden arising from prevalent cases into account are warranted. Second, other costly comorbid conditions that were not accounted for via the CCI in the matching process may have influenced the cost burden estimates. Third, beyond determining the difference of costs with respect to the presence or non-presence of bronchiectasis, matching on the basis of an equivalent CCI score level does not allow to determine the costs of COPD or other diseases included in the CCI separately.

Fourth, although the number of insured persons from which bronchiectasis patients and their controls were taken was large at more than 4.8 million, our patients were not formally selected as part of a representative sample. Furthermore, our higher proportion of males with bronchiectasis, a disease considered more common in women than in men in Western countries, [27,28] may reflect the generally higher proportion of insured males in all age groups of our study population, which in 2012 included in total 614,744 more males than females in German health insurance funds [29]. Thus, it is not certain whether our results may be generalized to the entire German population. In addition, patients were only included in our analysis if they had no diagnosis of bronchiectasis within the 3 years prior to the coding date in 2012, and if they were continuously eligible for comprehensive health benefits in the 3 years following the diagnosis. Consequently, the figure of 6.1 newly diagnosed bronchiectasis patients per 100.000 insured persons in our sample is lower than those estimated in the recently published studies of Quint et al. [10] and Weycker et al. [11] with 21.2 and 29 incident cases per 100.000 person-years in the UK and the U.S., respectively.

Nevertheless, our results not only demonstrate that per patient spending on bronchiectasis is high but also suggest that efforts at providing earlier and more effective treatment are warranted with a view towards lowering both mortality and costs. Indeed, although the present findings have to be seen in the context of the German healthcare system, we expect that studies subsequently performed in other Western countries would arrive at similar economic conclusions. However, although European Guidelines have recently been published [26], they have not yet been implemented in Germany. However, national guidelines are desperately needed given the drastic risk of refund claims for costly off-label prescriptions from SHI companies, as indicated by the infrequent use of inhaled antibiotics in our “real life” study sample.

Conclusions

Although bronchiectasis is considered to be underdiagnosed, the mortality and the

associated financial burden in Germany are substantial. Efforts to manage bronchiectasis costs may be directed at reducing hospitalization expenditures, which are the main cost drivers. Providing early and effective therapeutic interventions that can prevent disease progression may further reduce the associated economic burden of bronchiectasis.

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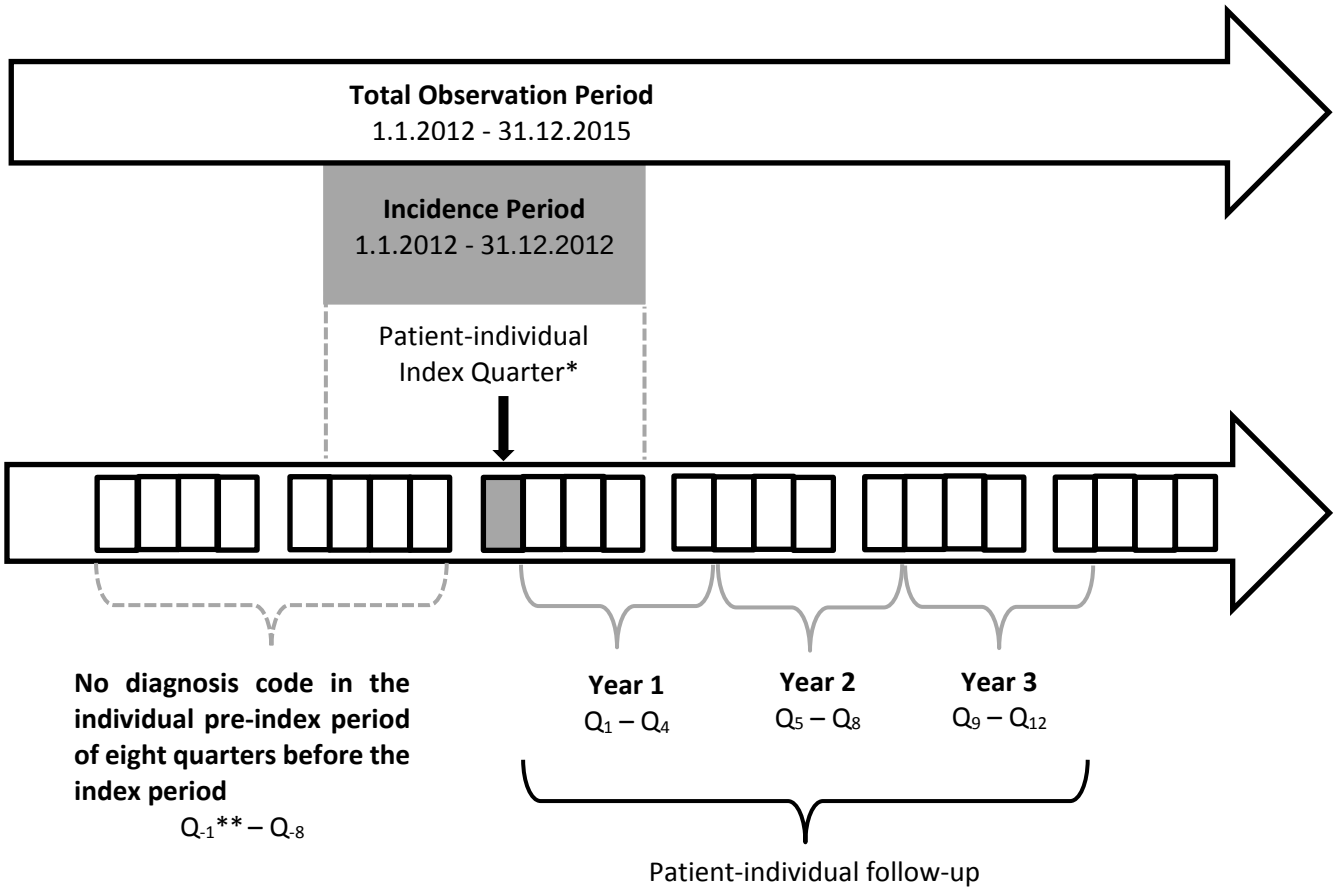
Figures

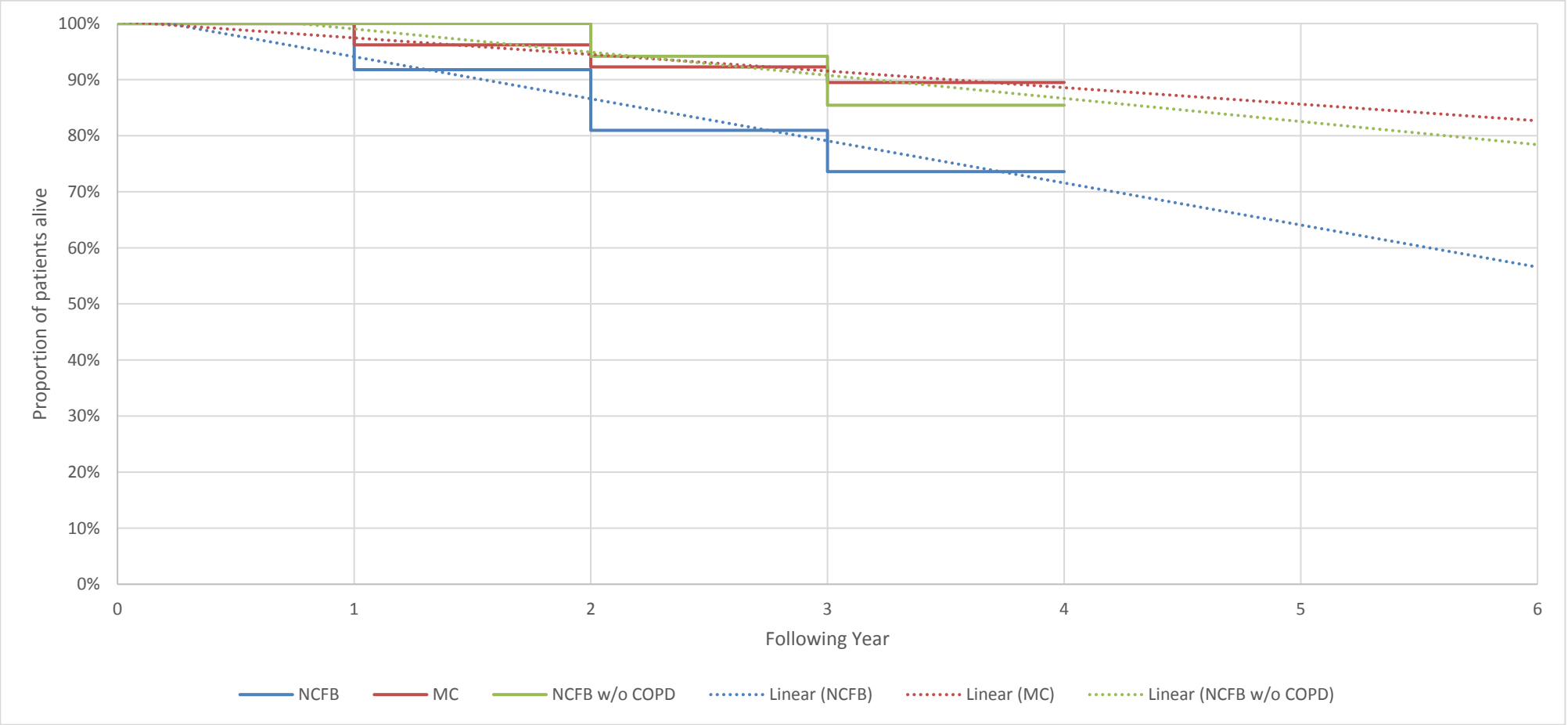
Figure 1. Patient-individual observation periods



*Example of a quarter of the first bronchiectasis diagnosis in 2012. Only verified diagnoses are considered in the outpatient setting whereas all types of diagnoses (primary and secondary diagnoses) are considered in the inpatient setting.

**All quarterly information refers to the patient-individual follow-up period relative to the index quarter.

Figure 2. Mortality rates among bronchiectasis patients, matched control (MC) patients and bronchiectasis patients without COPD within 36 months of observation



Tables

Table 1. Most frequent diseases out of the range of CCI comorbid conditions in bronchiectasis and matched control patients*

ICD-10-GM Code	Description	bronchiectasis patients (no.)	bronchiectasis patients (%)	Matched controls (no.)	Matched controls (%)	*P-Value*
J44.-	COPD	128	55.4	246	35.9	<.001
J45.-	Asthma	65	28.1	185	27.0	ns (0.78)
K21.-	Gastro-oesophageal reflux disease	34	14.7	101	14.7	ns (0.78)
M06.-	Other chronic polyarthritis	6	2.6	17	2.5	ns (1.0)
I25.-	Coronary Heart Disease	36	15.6	105	15.3	ns (0.77)
I50.-	Heart failure	27	11.7	69	10.1	ns (0.77)

*multiple entries are possible

ns: not significant

Table 2. Age- and gender-adjusted incidence rate of bronchiectasis patients included in the study

Age group (yr)	Gender	Patients (no.)	per 100.000*	Lower 95% CI	Upper 95% CI
< 15	female	0	0.00	000	0.00
15 to 65	female	863	3.66	3.42	3.91
> 65	female	1,036	11.38	10.71	12.10
total	female	1,899	5.13	4.91	5.37
< 15	male	124	2.74	2.28	3.27
15 to 65	male	903	4.03	3.78	4.31
> 65	male	1,390	21.68	20.57	22.86
total	male	2,417	7.25	6.97	7.55
< 15	total	124	1.40	1.17	1.68
15 to 65	total	1,766	3.84	3.66	4.03
> 65	total	2,426	15.64	15.03	16.28
total	total	4,316	6.14	5.96	6.32

*per 100,000 persons under risk. Incidence rate refers to a population of 4,850,013 insured members who could be followed for the entire period of 36 months.

Table 3. Total cost of bronchiectasis and costs separated by main cost types compared with matched controls after adjusting for age, sex, and Charlson Comorbidity Index scores

	Control group without bronchiectasis (*N*=685)			**Incident bronchiectasis patients (*N*=231)**			**Ratio of the mean (RoM)**		***P*-Value****
	Sum (€)	**Mean (€)‡**	**95% CI**	**Sum (€)**	**Mean (€)‡**	**95% CI**	**RoM**	**95% CI**	
Outpatient diagnostic and visiting costs*	1,840,235.71	2,792.47	2,699.33 - 2,885.61	632,567.17	2,983.81	2,795.81 - 3,171.81	1.07	0.995-1.15	ns (0.27)
Costs of remedies*f****	158.094,73	239.9	215.44 - 264.36	82,556.87	389.42	301.68 - 477.16	1.62	1.27-2.08	0.02
Medical aids costs‡***	259,848.97	394.31	300.36 - 488.26	230,186.30	1,085.78	809.87 - 1,361.69	2.75	1.95-3.90	<.001
Sick pay costs¥	14,603.98	22.16	16.33 - 27.19	4,586.89	21.64	12.63-30.65	0.98	0.60-1.60	ns (0.8)
Hospitalization costs	2,757,026.84	4,183.65	3,577.8 - 4,789.5	1,378,925.53	6,504.37	5,098.02 - 7909.82	1.56	1.20-3.01	<.001
Drug costsƃ***	4,352,366.43	6,604.5	3,757,13 - 9,451,87	1,621,706.53	7,694.56	53,54.77 - 9,944.35	1.16	0.69-1.95	ns (0.67)
Costs of antiobstructive medication***	704,490.03	1,069.03	917.46 - 1,136.46	338,229.90	1,595.42	1,444.88-2,048.6	1.49	1.37 - 1.52	<.001
Costs of antibiotics***	56,691.69	85.31	77.80-92.82	87,727.50	413.81	176.28-651.34	4.85	2.72-8.64	<.001
Costs of mucoactive agents	9322.73	14.15	10.51-16.79	14,863.81	70.11	51.65-88.57	4.96	4.91-5.28	.001
Total cost	9,382,176.66	14,236.99	11,318.87 - 17,155.21	3,950,529.29	18,634.57	15,891.02 - 23,871.13	1.31	1.02-1.68	<.001

CI: Confidence interval; RoM: Ratio of the mean

* Outpatient costs comprise reimbursement for outpatient physician´s office visits, laboratory diagnostics and imaging

** Wilcoxon-Mann-Whitney (two-sided)

*** as outpatients

ƒ Remedies comprise physiotherapy treatments and modalities such as active cycle of breathing and postural drainage techniques

† Medical aids comprise nebulizers and respiration therapy equipment

¥ Sick pay is paid out in the SHI as a substitute wage from day 43 of the sick leave according to §44 of the 5th German Social Code (SGB V).

ɒ Prescribed pharmaceuticals according to German national drug (ATC) codes

‡ adjusted to patients who died during the observation period

Table 4. Disease-related event numbers for bronchiectasis patients compared with matched controls

	Control group without bronchiectasis (*N*=685)			Incident bronchiectasis patients (*N*=231)			Ratio of the mean		*P*-Value**
	Sum	**Mean**	**95% CI**	**Sum**	**Mean**	**95% CI**	**RoM**	**95% CI**	
No. outpatient appointments	15,427	23.41	22.8-24.02	5,230	24.67	23.32-26.01	1.05	0.99-1.12	ns (0.12)
No. outpatient appointments (general practitioner)	5,479	9.83	9.6-10.02	631	9.18	8.77-9.59	0.93	8.77-9.59	0.002
No. outpatient appointments (chest physicians)	901	1.37	1.22-1.52	901	2.51	2.24-2.78	1.83	1.57-2.14	<.001
No. outpatient appointments (cardiologists)	488	0.74	0.66-0.82	172	0.81	0.55-0.95	1.10	0.90-1.33	ns (0.60)
No. outpatient appointments (radiologists)	1,490	2.26	2.12-2.35	612	2.89	2.57.-3.03	1.28	1.21-1.43	<.001
No. sick leave days	30,111	45.69	39.49-51.89	8,897	40.50	27.28-53.72	0.89	0.62-1.26	ns (0.18)
No. hospital days	9,746	14.79	13.92-15.66	4,163	19.64	15.96-23.32	1.33	1.09-1.61	<.001

CI: Confidence interval; RoM: Ratio of the mean

**Wilcoxon-Mann-Whitney (two-sided)

‡ adjusted to patients who died during the observation period

Table 5. Top 25 of prescribed drug for bronchiectasis patients compared to matched controls

ATC-Code	Agent	Percentage of prescriptions for bronchiectasis patients	Prescrip-tions (no.)	Rank	Prescriptions per bronchiectasis patient	Percentage of prescriptions for control patients	Prescrip-tions (no.)	Rank	Prescriptions per control patient	*P*-Value*
R03AC02	Salbutamol	30.66%	**449**	1	6.91	32.02%	**1.396**	1	6.62	ns (0.75)
R03AK07	Formoterol/Budesonide	22.64%	**334**	2	6.96	18.21%	**849**	4	7.08	ns (0.96)
J01CA04	Amoxicillin	21.23%	**95**	3	2.11	18.66%	**266**	3	2.16	ns (0.82)
J01MA02	Ciprofloxacin	20.75%	**105**	4	2.39	16.24%	**208**	5	1.94	ns (0.91)
R03BB04	Tiotropium bromide	19.34%	**342**	5	8.34	13.51%	**605**	7	6.80	ns (0.82)
J01DC02	Cefuroxime	17.92%	**117**	6	3.08	27.01%	**329**	2	1.85	ns (0.67)
J01CR22	Amoxicillin/Clavulanic acid	16.51%	**92**	7	2.63	8.80%	**103**	13	1.78	ns (0.45)
J01FA10	Azithromycin	15.57%	**87**	8	2.64	8.65%	**117**	14	2.05	**0.004**
R03AK06	Salmeterol/ Fluticason	14.62%	**257**	9	8.29	13.20%	**599**	9	6.89	ns (0.66)
R03BA02	Budesonide	14.15%	**176**	10	5.87	10.62%	**355**	10	5.07	ns (0.85)
J01FA09	Clarithromycin	12.74%	**57**	11	2.11	6.37%	**117**	16	2.79	ns (0.05)
J01AA02	Doxycyclin	12.26%	**52**	12	2.00	13.35%	**179**	8	2.03	ns (0.73)
R03AC13	Formoterol	11.32%	**181**	13	7.54	14.57%	**646**	6	6.73	ns (0.47)
R01AD09	Mometason	10.85%	**112**	14	4.87	5.31%	**120**	19	3.43	ns (0.41)
R05CB01	Acetylcysteine	10.38%	**133**	15	6.05	4.86%	**120**	21	3.75	ns (0.45)
R03AK03	Ipatropium bromide/Fenoterol	9.91%	**141**	16	6.71	5.92%	**316**	18	8.10	ns (0.89)
J01MA12	Levofloxacin	9.43%	**91**	17	4.55	9.41%	**120**	12	1.94	ns (0.57)
J01MA14	Moxifloxacin	8.96%	**43**	18	2.26	6.07%	**78**	17	1.95	ns (0.64)

J01FF01	Clindamycin	8.02%	**32**	19	1.88	10.32%	**139**	11	2.04	ns (0.89)
J01FA06	Roxithromycin	8.02%	**24**	19	1.41	8.19%	**113**	15	2.09	ns (1.0)
R03DA04	Theophyllin	6.60%	**96**	21	6.86	4.10%	**278**	24	10.30	ns (0.60)
J01CE02	Phenoxymethylpenicillin	6.60%	**28**	21	2.00	5.16%	**63**	20	1.85	ns (0.23)
J01EE01	Sulfamethoxazol/ Trimethoprim	6.60%	**38**	21	2.71	4.25%	**64**	23	2.29	ns (0.09)
R03BB05	Aclidinium	6.13%	**48**	24	3.69	1.82%	**65**	26	5.42	**0.002**
R03BB01	Ipratropium bromide	6.13%	**72**	24	5.54	2.28%	**70**	25	4.67	ns (0.83)

*Chi-square testing

Table 6. Unadjusted mortality rates by follow-up years

Group	Time	Patients at risk	Patients diseased	Mortality
Control	Year 1	685	26	3.80%
	Year 2	659	27	4.10%
	Year 3	632	19	3.01%
	Total	685	72	10.51%
Bronchiectasis	Year 1	231	19	8.23%
	Year 2	212	25	11.79
	Year 3	187	17	9.09%
	Total	231	61	26.41%
Bronchiectasis w/o COPD	Year 1	103	0	0.0%
	Year 2	103	6	5.83%
	Year 3	97	9	9.28%
	Total	103	15	14.56%